REMARKS

Status of the Claims

Claims 7, 11, 12, 14, 19, 22-27, 30, 32-37, 41, 42, 46-48, 51-54, 59, 66, 69-70, 72-94, 97-128 are pending in the present application.

Interview Summary Record

Applicants thank the Examiners for their time during the recent interview. During the interview, Applicants pointed out to the Examiners that substantially similar claims, as amended, were allowed by the European Examiner and the corresponding European Application has issued as a patent. A copy of the European patent is attached. Since the standards for novelty and inventive step [e.g. obviousness] are relatively similar in both Europe and in the U.S., the current rejections are unreasonable and should be withdrawn.

Applicants further argued that for the research leading to the present invention, and at the time that the present invention was made, Applicants purchased HA from suppliers that based molecular weight on intrinsic viscosity. Further, Applicants tested the molecular weight of the HA based on the protein standard rather than the Dextran standard. The Dextran standard was recognized as an inferior standard at the time of the invention, contrary to the teachings of Turley. [See attached Declaraton of the inventor.] This is why Applicants conducted testing with the more accurate protein standard, which produces the same results as the art recognized intrinsic viscosity, the accepted "gold standard" at the time of the invention (and currently.) Indeed, at the time that the invention was made and through the present time, the vendors sell

their product in terms of intrinsic viscosity. Thus, at the time that the invention was made, researchers were most likely to use the instrinsic viscosity standard, wherein the same values are obtained by the more easy to run test using the protein standard.

Further, even in the Turley et al patent intrinsic viscosity is provided in the HA specifications that are cited. The intrinsic viscosity of the HA preparations that Turley et al cites range from 4.5 to 14.5 dl/g. An intrinsic viscosity of 14.5 relates to a molecular weight of 750,000 daltons. The intrinsic viscosity for the at least one high molecular weight fraction of HA cited in the present invention (>1,000,000 daltons) is >17.2 dl/g. Therefore, it is clear that the >1,000,000 dalton fraction in the present invention is outside the range taught by Turley et al. Indeed, Turley et al. expressly teach away from Applicants' claimed range.

Claim Objections

Claims 66 and 117 have been amended to address the matters raised by the Examiner.

Rejection of Claims 122 and 123 Under 35 U.S.C. 112, First Paragraph

Claims 122 and 123 are rejected by the Examiner under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

Claims 122 and 123 have been amended to address the matters raised by the Examiner. Accordingly, this rejection should be withdrawn.

Rejection of Claim 49 Under 35 U.S.C. 112, first paragraph

Claim 49 has been rejected by the Examiner under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. This new rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

In view of the extended prosecution in the present application, such new rejections are unreasonable and amount to piecemeal prosecution. At this stage, claim 49 has been cancelled to obtain a quick allowance of the present application. Similarly, Applicants are removing the cancer prevention and treatment from all other claims in order to expedite prosecution. Accordingly, the rejection under 35 USC 112, first paragraph, should be withdrawn by the Examiner.

Claim Rejections - 35 U.S.C. §102

Claims 2, 3, 6, 7, 19, 22, 23, 26, 37, 41, 42, 46-51, 53, 54, 59, 66, 70, 72-76, 91-94, 112, 113, 115 and 117-127 are rejected by the Examiner under 35 U.S.C. 102(b) as being anticipated by WO 97/25051 to Turley. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

In order to overcome this rejection, Applicants again point out how molecular weight was measured by the inventors and reported by the suppliers based on their Certificates of Analysis. For instance, see page 16, line 25+ of Applicants WO 00/44367. One of ordinary skill in the art at the time that the invention was made would utilize intrinsic viscosity and/or the more easily run test using the protein standard.

The Examiner cites Turley et al (WO 97/25051, 1997) as disclosing a product comprising a hyaluronic acid fraction having a molecular weight in the range of about 30,000 to 2 million Daltons (page 5, lines 4-28). It should be noted that within this statement is the qualification on line 23-27 " detected by Dextran Standards (which corresponds to between about 9,000 daltons and about 600,000 daltons delivered by the Protein Standard using the conversion factor of about 3.3)." The claims of the current invention recite the composition as having at least one fraction with a molecular weight >1,000,000, which were measured using a protein standard and purchased on the basis of intrinsic viscosity, the latter being a more universally used measurement of the molecular weight of polymers, including HA, and statistically correlates with the Protein Standard as shown in the graph below (Figure 1). Certificates of Analysis supplied with purchases of hyaluronic acid (prior to Turley et al and at present) list the Intrinsic Viscosity as a measure of the molecular weight.

Intrinsic Viscosity is listed routinely in Turley where it appears that she is listing the testing reported on the Certificates of Analysis from her suppliers (see page 7, line 15, where the Intrinsic Viscosity is stated as 4.5 - 11 dL/g; page 8, lines 10-13, the Intrinsic Viscosity is stated as 10.0 and 14.5 deciliters per gram and the molecular weight based on the Intrinsic Viscosity is 500,000 to 800,000 daltons; page 9, lines 9-13, the Intrinsic Viscosity is between 11.5 and 14.5 deciliters per gram and the molecular weight is 600,000 and 800,000 daltons based on the Protein Standard and Intrinsic Viscosity; page 11, lines 18-19 a preparation from Lifecore™ Biomedical is described as having a Viscosity Average of <750,000 Daltons using a Protein Standard). In fact, every preparation cited identifies the Intrinsic Viscosity, Viscosity Average and/or Protein Standard.

Intrinsic Viscosity of HA is related to the molecular weight using the art-known Mark-Houwink Equation.

MW = (intrinsic viscosity*100/.036)^(1/.78)

intrinsic viscosity = (MW^.78)*.036/100

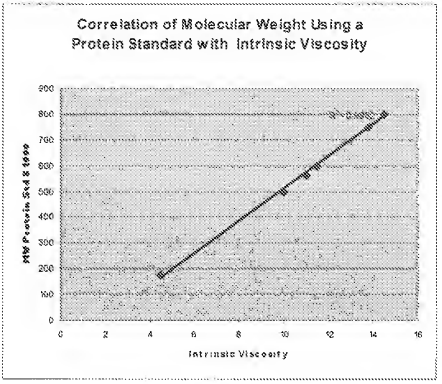
Mark-Houwink Equation:

The preparations cited by Turley et al, demonstrated Intrinsic Viscosity values from 4.5 to 14.5 dl/g. Inserting the Turley et al Intrinsic Viscosity values into the Mark Houwink Equation gives a molecular weight range for the Turley preparations between 166,857 and 747,870 Daltons. This correlates well with the molecular weight range that Turley claims when basing her numbers on the Protein Standard.

When the Intrinsic Viscosity values and the molecular weight values (as determined using the protein standard) for the four sources of HA cited in Turley et al are compared in a scatter chart, the result is the graph shown in Figure 1. This graph demonstrates that the

correlation between the molecular weight as measured using a Protein Standard and the Intrinsic Viscosity are statistically significant with a $R^2 = 0.9982$. A perfect correlation is 1.000.

Figure 1 Use of Turley et al Data to Demonstrate Correlation Between the Protein Standard and Intrinsic viscosity



The HA fraction >1,000,000 Daltons claimed in the present invention would have an Intrinsic Viscosity of > 17.2 dl/g. The values in the present claims were measured using a protein standard which provides the same values as Intrinsic Viscosity.

Finally, on page 12, lines 11- 15, Turley clearly teaches away from use of molecular weights of 1,000,000 daltons or greater. "Recently, it has been found that large molecular weight hyaluronic acid having a molecular weight exceeding about 1,000,000 daltons, self-aggregates and thus, does not interact very well with HA receptors. Thus, the higher molecular weight hyaluronic acid should be avoided (such as Healon™)".

Previously, the Examiner states that:

> The molecular weight of the hyaluronic acid can range from 30,000 to 2,000,000 Daltons, thereby encompassing all of the molecular weight fractions recited in the rejected claims.

The Examiner's technical analysis is factually in error and confuses the protein and dextran standards. It is well known in the art that 30,000 to 2,000,000 Daltons using the dextran standard of Turley is well below the 1,000,000 dalton limitation using the protein standard. For instance, 2,000,000 Daltons using the dextran standard is about 650,000 Daltons using the protein standard. See page 25 of Turley.

The Examiner's attention is again directed to the Rule 132 Declaration attached to Applicants prior Reply. Indeed, the European Examiner was convinced by this Declaration and allowed the claims.

More specifically, as stated in the prior Rule 132 Declaration, for the research leading to the present application and at the time that the present application was prepared, Applicants based the molecular weight measurements on the protein standard rather than the dextran standard. [The protein standard is easier to run and gives the same results as intrinsic viscosity.] The specific method used was size exclusion chromatography (gel permeation chromatography or HPLC) and the protein standards were Immunoglobulin M, with a molecular weight of 900,000 daltons, Thyroglobulin with a molecular weight of 670,000 daltons, Gamma globulin with a molecular weight of 158,000 daltons and Ovalbumin with a molecular weight of 44,000 daltons. Using this method, one of the complex carbohydrates used by applicants as an example of an effective high molecular weight component was confirmed to have a molecular weight greater than 1,000,000 daltons by a third party laboratory, using the same protein standards (see attached document titled "Certificate of Analysis No. 030791).

Accordingly, Turley does not teach or suggest the present invention.

Claim Rejections - 35 U.S.C. §103

The Examiner has rejected claims 2, 3, 6, 7, 11-14, 19, 22, 23, 36, 37, 41, 42, 46-51, 53, 54, 59, 66, 69, 70, 72-90, 91-94, 112, 113, 115 and 117-127 under 35 U.S.C. 103(a) as being unpatentable over Turley et al (WO 97/25051 1997) as applied to claims 2, 3, 6, 7, 19, 22, 23, 36, 37, 41, 42, 46-51, 53, 54, 59, 66, 69, 70, 72-76, 91-94, 112, 113, 115, and 117-127 with support from Sharma et al (U.S. Patent #4,933,163, 1990) and Weitzberg et al (U.S. Patent # 5,079,260). Claims 2, 3, 6, 7, 9, 11-14, 19, 22, 23, 36, 37, 41, 42, 46-51, 53, 54, 59, 60, 69, 70, 72-90, 91-94, 112, 113, 115, and 117-127 have been rejected under U.S.C. 103(a) as being unpatentable over Turley et al as applied to claims 2, 3, 6, 7, 11-14, 19, 22, 23, 36, 37, 41, 42, 46-51, 53, 54, 59, 66, 69, 70, 72-90, 91-94, 112, 113, 115, and 117-127 above, and further in view of Gaeta et al (U.S. Patent 5,559,103, 1996), using the same molecular weight basis as the early rejections based on Turley. These rejections are traversed for the reasons stated above and for the reasons of record.

Applicants' remarks with respect to the rejection under 35 U.S.C. 102 are equally applicable here and are herein incorporated by reference.

The Examiner's technical analysis is factually in error and confuses the protein and dextran standards. It is well known in the art that 30,000 to 2,000,000 Daltons using the dextran standard of Turley is well below the 1,000,000 dalton limitation using the protein standard. For instance, 2,000,000 Daltons using the dextran standard is about 650,000 Daltons using the protein standard. See page 25 of Turley.

Indeed, Turley et al. teaches away from the present invention when she clearly states that a molecular weight >1,000,000 daltons will not be orally effective (see page 12, lines 8-14). In

fact, Turley et al. teach away from using any composition with a molecular weight >1,000,000 daltons. In the present invention, one of the molecular weight fractions recited by the amended claims is >1,000,000 daltons.

The Examiner's reliance upon the secondary reference(s) does not correct this deficiency.

The Examiner rejects claim 9 in view of Gaeta et al. Claim 9 has been cancelled.

In view of the comments hereinabove, the rejections should be withdrawn.

Rejoinder

Rejoinder of the method claims is requested.

CONCLUSION

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Marc S. Weiner (Reg. No. 32,181) at the telephone number of (703) 205-8000, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any

additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Dated: JUL 25 2007

Respectfully submitted,

By _____

Marc S. Weiner
Registration No.: 32,181
BIRCH, STEWART, KOLASCH & BIRCH, LLP
8110 Gatehouse Road
Suite 100 East
P.O. Box 747
Falls Church, Virginia 22040-0747
(703) 205-8000
Attorney for Applicant

Attachments: Declaration (§132)
EP 1165097